CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40183

CORRESPONDENCE

ANDA 40-183

Vintage Pharmaceuticals, Inc.
Attention: Rebecca A. Thurman
3241 Woodpark Blvd.
Charlotte NC 28206

JUL 5 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Methylprednisolone Tablets USP, 4 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs.

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   NLT % of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, ~~Ph.D.~~
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-183

Vintage Pharmaceuticals, Inc.
Attention: Rebecca A. Thurman
3241 Woodpark Blvd.
Charlotte, NC 28206

18 1996

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated February 29, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Methylprednisolone Tablets USP, 4 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> You have failed to completely package your exhibit batch in containers proposed for marketing. Partial packaging, packaging into bulk storage containers, or a packaging configuration for which you are not seeking approval is not acceptable unless a protocol has been submitted and approved prior to submission of the application. For instance, your records show a % yield but you appear to have packaged tablets, less than the minimum packaging required. Please refer to the letters to the industry from the Director, Office of Generic Drugs, dated November 8, 1991, and August 4, 1993. In addition, we refer you to the Office of Generic Drugs' Policy and Procedure Guide #41-95, dated February 8, 1995.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Project Manager
(301) 594-0315

Sincerely yours,

/S/ 3/18/96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-183
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief,RSB /S/ 3/15/96 date
HFD-615/WRussell, CSO /S/ date 3/17/96
HFD-623/ARudman, Dep. Dir. date
File\x:\new\firmsnz\Vintage\ltrs&rev\40183rtf.f
F/T File hrw 3-14-96
ANDA Refuse to File!

ANDA 40-183

Vintage Pharmaceuticals, Inc.
Attention: Rebecca A. Thurman
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Madam: APR 10 1996

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated March 18, 1996, and your amendment dated March 22, 1996.

NAME OF DRUG: Methylprednisolone Tablets USP, 4 mg

DATE OF APPLICATION: February 29, 1996

DATE OF RECEIPT: March 5, 1996

DATE ACCEPTABLE FOR FILING: March 25, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

James Wilson
Project Manager
(301) 594-0310

Sincerely yours,

4/10/96

/S/
Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

5. **You have specified the location of the manufacturing of this product (page 1281) but did not specify if this includes the packaging, labeling, stability testing, etc. Please clarify.**

Attachment XXIII - Revised page 1281

6. **We highly recommend a retest data of one year for actives and two years for inactives.**

Attachment XXIV - Section X of revised raw material testing SOP

7. **Please explain why you have included Letters of Authorization for DMF and DMF These liners are not included in the Section XIV-Summary of Container/Closure Systems.**

Attachment XXV - Revised Summary of Container/Closure Systems

The above mentioned liners should not have been included. These liners are for use with closure systems. The Vintage closures are

This concludes our response to the deficiencies. If we can be of further assistance, or if you have any question, please contact myself or John Schultz at (704) 596-0516.

Sincerely,

Rebecca Thurman
Regulatory Affairs Manager

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

January 7, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: Amendment, ANDA 40-183
Methylprednisolone Tablets, USP 4 mg
Major Amendment

Dear Sir:

Please refer to our original ANDA, submitted February 29, 1996, our amendment dated March 22, 1996, and your letter dated September 13, 1996.

Below, please find our response to each of the deficiencies listed in your letter.

A. Chemistry Deficiencies

Observation:

1. **"Please revise and resubmit your 356H form to include all related NDA and DMF information."**

Response:

Attachment I - Copy of Form 356H as submitted in the original submission dated February 29, 1996. Two DMF references have been crossed-out due to their withdrawal in response to item #7 under additional information.

Observation:

2. **"Please revise the release specifications for the drug substance to include specifications for individual (known and unknown) and total impurities (known and unknown).**

Response:

Attachment II - Revised release specifications

Observation:

3. **The Certificate of Analysis from the drug substance supplier specifies that the methylprednisolone is micronized. Your information in the raw material controls section does not reflect this, however, your batch records do. Please revise your Certificate of Analysis for the drug substance to specify "micronization". Also include a test and specification for particle size as part of the release specifications.**

Response:

Attachment III - Revised Certificate of Analysis.
Attachment IV - Revised release specifications

Observation:

4. **"The test batch was manufactured on 04-24-95. The COAs for the excipients indicate that they were analyzed on 02-06-96. Please explain this delay."**

Response:

The excipients were tested upon receipt, however COAs were not generated. The data was recorded on the receiving report. The formal COA was generated in February 1996 for the purposes of this ANDA submission. Future COAs will have prepared by instead of release by.

Attachment V - Receiving reports and revised COAs that show original release date and prepared by date

Observation:

5. **"Your reprocessing procedure to add excipient to correct physical tablet attributes (granulation sticking or picking to tableting punch) is not acceptable because it indicates lack of adequate controls in the manufacturing process. Please establish controls in your manufacturing process to avoid this problem.**

Response: *It is our understanding that SUPAC will allow for the addition of certain types of excipients at established maximum levels to correct a physical tableting attributes providing they are already in the formulation. We do not intend for this procedure to include the milling or grinding of compressed tablets for reblend and are aware this type of reprocessing does require the agency's prior approval. We do believe the controls in our manufacturing process are adequate to prevent tableting problems and have preformulation, pilot and validation data to support this, but we also want to be prepared for any unforseen situations that may arise. We will, however, follow any directive issued by the FDA.*

Observation:

6. **The COA for the 100 cc bottle (page 1456) from specifies the resin color added is a This is inconsistent with the Letter of Authorization from which specifies Please explain.**

Response: *The resin color was incorrect on the COA. The correct description is which is the same as the The represents and represents The description was shortened on the COA.*

Attachment VI - Corrected COA
Manufacturer's COA
Information Sheet

Observation:

7. **Please provide a drawing for the configuration of the molded finished blister package. If it is multiple-layers, please include a drawing indicating layer thicknesses and layers in contact with the drug product.**

Response:

The product is in a single layer within the blister cavities. The product only comes in contact with the foil backing and the PVC/Aclar.

Attachment VII - Actual molded blister cards

Observation

8. **You have provided the QA Inspection Reports for the packaging components. Are these equivalent to Certificates of Analysis? If so, Please include tests and specifications for incoming identification (such as IR and/or DSC) and conformance to a drawing or master sample. If they are not COAs, please provide the COAs for each lot of packaging components used in this test batch.**

Response *The QA inspection reports are equivalent to a COA. The master has been revised to include identification testing for incoming components. Specifications on the QA inspection reports are taken directly from the drawings.*

Attachment VIII - Inspection Reports, Drawings and Scans for HDPE containers, caps, PVC

Observation

9. **Your tablet in-process hardness specification is but your release and stability specification is NLT Please revise the release and stability specification to include an upper limit and provide data to support this specification. Data is being submitted to support these hardness specifications.**

Note: The data is from a batch that is not the submitted batch in this application. The batch is the same formulaton however, the source of the active ingredient is different. This batch will be submitted at a later date as a supplement to this application.

Response *Attachment II - Revised release specifications*
Attachment IX - Revised stability protocols
Attachment X - Dissolution data supporting hardness limits

Observation

10. **Please include blend uniformity testing as a permanent in-process control and include the results on the in-process certificate of analysis**

Response *Attachment XI - In-process certificate of analysis*
Attachment XII - Master Batch Production Record
page 4 of 8 contains sampling instructions

Observation

11. **Please reduce your individual and total impurities (known and unknown) specifications for finished drug product release and stability to more accurately represent your data.**

Response *Attachment II - Revised Finished Product Specifications*
Attachment IX - Revised Stability Protocols
Attachment XIII - Revised Stability Reports

Observation

13. **In order to support your expiration period of 36 months, you must provide shelf-life data up to 36 months. Three months or any additional accelerated stability data only supports a tentative two year expiration period.**

Response *Attachment XIV - Revised Proposed Expiration Date Request*

Observation

14. **Please revise your Long-Term Stability Commitment to specify that "Yearly, one lot of the smallest and largest size of each container/closure system will be added to the stability program".**

Response *Attachment XV - Revised Stability Commitment*

Observation

16. **Please explain the disappearance of the impurity 6-alpha-methylhydrocortisone over time, as noted in the stability reports (room temperature and accelerated conditions for any packaging configuration).**

Response *The method was re-investigated and it became evident that over time (approximately 20 injections) the column cannot produce sufficient resolution between impurity peaks. Because of this analysts have difficulty correctly identifying and quantifying individual impurities. To correct this problem and to ensure all impurity peaks are properly identified and calculated, Vintage has revised the method for the methylprednisolone impurities assay. The new procedure is based on the impurity procedure used by the Raw Material Supplier which was not available to Vintage at the time of the intial methods validation. As a result of the impurity investigation three more known impurities were found.*

Attachment XVI - Revised laboratory procedure
Attachment IX and XIII - Revised stability protocols and forms
Attachment II - Revised Release specifications
Attachment XVII - Supplement to Methods Validation

Observation

17. **Please revise your Post Approval Stability Commitment to specify that the results will be reported annually via annual reports**

Response *Attachment XV - Revised Stability Commitment*

Observation

18. **Your description of the product on the COA and stability reports specifies embossing and quadrisection of the tablet, but the description in the HOW Supplied section of the label specifies debossing and no quadrisection. Please explain this difference.**

Response *The COAs, stability report and insert should describe the tablet as debossed and quadrisected.*

Attachment II - Revised COA
Attachment XVIII - Revised insert

B. Labeling Deficiencies

1. CONTAINER (100's, 500's and 1000's)

Satisfactory in draft

2. UNIT-OF-USE BLISTER PACK
Satisfactory in draft (21's)

3. CARTON

Your proposed draft carton labeling appears to be a packaging configuration for several unit-of-use blister packs. Please revise the labeling to include the quantity statement (e.g. 5 UNIT-OF-USE PACKS) or comment.

Attachment XIX - Revised carton drafts

4. INSERT

a. ACTIONS - Revise the section heading to read;

CLINICAL PHARMACOLOGY

b. INDICATIONS - Revise the section heading to read'

INDICATIONS AND USAGE

c. HOW SUPPLIED

i. According to your description of the finished dosage form (p. 1538) your products are quadrisected and embossed with "42/16/V" on the upper and with "4" on the ...

..., oval, quadrisected tablets embossed "42/16/V on the upper and "4" on the ...

[Note: "embossed" rather than "debossed", "42/16/V" rather than "4216/V". We encourage you to use the term "quadrisected" rather than "scored".]

ii. We encourage you to include the NDC numbers

iii. "unit-of-use packs" rather than "unit dose packs"

Attachment XVIII - Revised inserts

Please revise your labels and/or labeling, as instructed above, and submit in final print or draft, if you prefer.

Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a)(8)(iv), please provide a side-by-side comparison with your last submission with all differences annotated and explained.

Attachment XX - Side-by-side comparison

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. **Please note that on page 1256 you specify Microcrystalline Cellulose as USP and it should be specified as NF.**

   Attachment XXI - Revised page 1256

2. **The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with CGMPs at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.**

3. **The specifications and tests for excipients should be updated to the current USP specifications.**

   Attachment XXII - Revised specifications and tests for excipients
   Microcrystalline Cellulose
   no other updates required for the excipients

4. **All DMFs referenced in this ANDA have to be found satisfactory at the time of approval of the ANDA. Some of the DMF holders may have to be inspected by our Division of Manufacturing and Product Quality. Any unsatisfactory review/evaluation will delay the approval of the ANDA.**

5. **You have specified the location of the manufacturing of this product (page 1281) but did not specify if this includes the packaging, labeling, stability testing, etc. Please clarify.**

Attachment XXIII - Revised page 1281

6. **We highly recommend a retest data of one year for actives and two years for inactives.**

Attachment XXIV - Section X of revised raw material testing SOP

7. **Please explain why you have included Letters of Authorization for DMF and DMF These liners are not included in the Section XIV-Summary of Container/Closure Systems.**

Attachment XXV - Revised Summary of Container/Closure Systems

The above mentioned liners should not have been included. These liners are for use with closure systems. The Vintage closures are

This concludes our response to the deficiencies. If we can be of further assistance, or if you have any question, please contact myself or John Schultz at (704) 596-0516.

Sincerely,

Rebecca Thurman
Regulatory Affairs Manager

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

ORIG AMENDMENT

September 19, 1997

Office of Generic Drugs
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: Minor Amendment , ANDA #40-183
Methylprednisolone Tablets, USP
4 mg

TELEPHONE AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted February 29, 1996 and our amendments dated March 22, 1996, June 6, 1996, January 7, 1997 and August 28, 1997.

As requested in your phone call of September 9, 1997, please find enclosed the following:

- 12 copies of the blister labeling as it will appear on the molded blister
- A sample of a molded blister

This completes our response to the telephone amendment issued. If I can be of further assistance or if you have any questions, please contact Rebecca Thurman or John Schultz at (704) 596-0516.

Sincerely,

Rebecca Thurman
Manager, Regulatory Affairs

RECEIVED

SEP 23

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

NDA [illegible] AMENDMENT
N/FA

October 3, 1997

Office of Generic Drugs
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RECEIVED
OCT 6 1997
GENERIC DRUGS

RE: Minor Amendment , ANDA #40-183
Methylprednisolone Tablets, USP
4 mg

TELEPHONE AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted February 29, 1996 and our amendments dated March 22, 1996, June 6, 1996, January 7, 1997, August 28, 1997, September 19. 1997 and September 24, 1997.

As requested in your phone call of October 2, 1997, please find enclosed the following:

- Methylprednisolone specifications (Attachment I)

  Total degradants/impurities has been revised to NMT %

- Revised finished product specifications (Attachment II)

  The total degradants/impurities (known and unknown) has been set as NMT %

  The specification for U-82,805 has been tightened to NMT %

- Stability data reports (Attachment III)

  The total degradants/impurities (known and unknown) has been set as NMT %

  The specification for U-82,805 has been tightened to NMT %

This completes our response to the telephone amendment issued. If I can be of further assistance or if you have any questions, please contact Rebecca Thurman or John Schultz at (704) 596-0516.

Sincerely,

Rebecca Thurman
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

ORIG AMENDMENT
10/F4

September 24, 1997

Office of Generic Drugs
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RECEIVED
SEP 2 5 1997
GENERIC DRUGS

RE: Minor Amendment , ANDA #40-183
Methylprednisolone Tablets, USP
4 mg

TELEPHONE AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted February 29, 1996 and our amendments dated March 22, 1996, June 6, 1996, January 7, 1997, August 28, 1997, and September 19. 1997.

As requested in your phone call of September 19, 1997, please find enclosed the following:

- Revised in-process testing specifications for granulation final blend (Attachment I)

- Laboratory test method for testing of the granulation final blend (Attachment II)

- Methylprednisolone specifications (Attachment III)

  The related substances have been broken down into process impurities and degradants. Each has been given a total limit of NMT % to match the raw material manufacturer. A total combined limit has been given of NMT % due to the fact that there are known degradants in the raw material.
  The retest date has also been changed to 6 months based on recommendations by the manufacturer. The manufacturer has based this retest date on the potential for potency degradation and the slightly greater rate of degradation for the micronized material.

- Revised finished product specifications, separating out the impurities and the degradants. (Attachment IV)

- Revised stability specifications, separating out the impurities and the degradants. (Attachment V)

This completes our response to the telephone amendment issued. If I can be of further assistance or if you have any questions, please contact Rebecca Thurman or John Schultz at (704) 596-0516.

Sincerely,

Rebecca Thurman
Manager, Regulatory Affairs

ark Blvd.
C 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

NDA ORIG AMENDMENT
N/AM

RECEIVED
NOV 13 1997
GENERIC DRUGS

November 12, 1997

Office of Generic Drugs
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: Minor Amendment , ANDA #40-183
Methylprednisolone Tablets, USP
4 mg

MINOR AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted February 29, 1996 and our amendments dated March 22, 1996, June 6, 1996, January 7, 1997, August 28, 1997, September 19. 1997, September 24, 1997 and October 3, 1997.

Below are listed the deficiencies as listed in your letter of November 3, 1997. Following each deficiency are the Vintage responses.

A. Deficiencies

1. The 11-ketomethylprednisolone is listed as an impurity in the drug substance with a specification of %. However, the finished product and stability specifications for this impurity have been increased to nmt %. Impurities should not increase on stability. Please revise your specification for the 11-ketomethylprednisolone at release and on stability to be consistent with that in the drug substance.

Attachment I - Revised release specifications
Attachment II - Revised accelerated stability reports
Attachment III - Revised room temperature stability reports (page 2 of each report)

Nadine 11.17.97

2. The following comments are related to the room temperature stability data that has been provided for the package size of 100's (attachment III of the 10/03/97 amendment):

a. You specify that some of the impurities were not tested because the testing procedure did not include these impurities, however, this information was provided for the accelerated studies. Please clarify this statement.

The initial investigation of the impurity method in was in response to the major deficiency dated 9/13/96. In this deficiency letter, it was asked why 6-alpha-methylhydrocortisone, which was % for a 2 month accelerated timepoint, had dropped to % at the three month accelerated timepoint. This was a clear indicator of a problem that was not caught by our Quality Control lab.

Upon investigation of the impurity method, we found:

a) that as a column became older and resolution was not as good, it became very difficult to correctly identify impurity/degradant peaks. This caused mislabelling of known impurities and, consequently, inconsistent results over stability testing timepoints.

b) Also, impurity samples proved to be very unstable in sample preparations causing more degradation the longer the time before the samples were analyzed. This also caused some inconsistent results over stability testing timepoints.

At that time the best course of action seemed to be to develop and validate a new impurity method that would be more reliable. The new method used for impurity testing, which was submitted as part of , is based on the raw material supplier's impurity method. The only changes made to their method were done to improve resolution between all known and unknown impurities/degradants.

The raw material supplier's impurity method contained nine known impurities/degradants. Our original method contained in contained only six out of these nine. We decided at that time to revise the new method to include all nine known impurities/degradants named by the raw material supplier.

The new impurity method was fully validated and proved to be extremely reliable and consistent. Results over impurity timepoints were no longer erratic as they were with the older impurity method. However, the new impurity method often gave different results for individual impurities than the old impurity method. For example,, the older impurity method may have determined 6-alpha-methylhydrocortisone for a certain lot of product as a specific timepoint to be %. Using the new method, the results for the same bottle of product would be % for 6-alpha-methylhydrocortisone. The discrepancy between the results indicated that the older method may not have accurately quantitiated all of the known impurities for reasons previously described. The results given by the newer method are considered the correct results for all duplicated stability timepoints.

With the new impurity method in place, we decided to re-analyze any stability timepoints possible. All of the initial and accelerated bottles and blisters of lot 069045A, 069045B, and 069045D, which were retained, were retested using the new impurity method . These timepoints give the worst case scenario for impurities because they were retested nearly a year after their original testing. Accelerated stability reports were updated to contain the new results for impurities found for these timepoints. All other data remained the same as tested according to the original method

Attachment II - Revised accelerated stability reports

Unfortunately, room temperature stability could not be treated the same way. The 3 month, 6 month, 9 month and 12 month room temperature results were all essentially 18 month room temperature samples by the time the new impurity method was developed. The room temperature stability reports were left to contain the impurity/degradant results determined by the original impurity method for these timepoints. At the 18 month timepoint, we altered out stability reports to include the nine impurities, new specifications and the total for impurities, degradants, and all known and unknown impurities/degradants. Also included was the revised initial impurity results as retested per the new lab procedure

Attachment III - revised room temperature stability reports

b. You indicate that the three month appearance test was not performed because the analytical test procedure was not available. It is not clear how an analytical test is involved in determining the description/appearance of the product. Please explain.

Since the analytical procedure was still in draft, the stability sample for the 3 month timepoint was not pulled for any testing including description and appearance.

c. There is no stability information at all for this product at the three month time point. Also, there is no degradants/impurities reported at the 12 month time point. Please explain why testing was neglected at these time points.

See response to b. for explaination of 3 month timepoint.

The 12 month impurities are missed due to analyst error. Analysis was not completed in a timely manner after the sample preparation for impurities resulting in bad data. This was not realized until time for the 18 month sample to be pulled, therefore re-prepping of the samples for 12 months was not done. The 18 month data shows the impurities to still be within specification limits.

d. Your data indicates out of specification results for 11-ketomethylprednisolone (0 and 6 month time points.), U-82,805 (0,6 and 9 month time points), 6- -methylhydrocortisone (0 and 6 month time points) and U-95,525 (0 month time point). Please explain how this product was released and entered into the stability program if it was out of specification at the initial time point. In addition, please explain if your data for the initial time point is the same as the finished product release data.

The data was not out of specification according to the analytical procedure in place at the time of testing, therefore, the product was released for the stability program. Since completion of stability the analytical procedure has been revised as detailed in the response to observation a.

Initially the finished product release data and the initial room temperature data were the same. The finished product release data has been revised to be the same as the initial as reported on the accelerated reports.

Attachment I - Revised finished product release
Attachment III - Revised room temperature stability reports

e. Please provide the investigation report for these out of specification results.

As stated in the response to d. the results were not out of specification at the time of testing, therefore no investigation was done.

f. The room temperature results for impurities/degradants is very inconsistent and in some cases, the data reports levels of % and then the next time point, the data is %. This fluctuation is beyond the experimental variation. The data reported for the accelerated studies is within specifications and very consistent throughout the studies. Please explain.

See explanation to observation a.

g. The stability reports should include the date the tests were performed.

Attachment II - Revised accelerated stability reports
Attachment III - Revised room temperature reports

h. Please explain why the total of all degradants and the total for all impurities were not reported for the room temperature stability studies.

Originally the total was not required. Beginning with the 18 month timepoint, totals are being reported.

Attachment III - Revised room temperature reports

i. Please provide the room temperature stability data for the other packaging configurations (1000's and blister)

Attachment III - Room temperature reports

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

On the cover letter of this amendment, you indicate that the specification for the U-85,805 is nmt ½, but the finished product specifications and the stability data reports specify nmt %. Please clarify.

The specification was incorrectly written in the cover letter. NMT % is correct.

This completes our response to the minor amendment issued. If I can be of further assistance or if you have any questions, please contact Rebecca Thurman or John Schultz at (704) 596-0516.

Sincerely,

Rebecca Thurman
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

NDA ORIG AMENDMENT

N/A M

December 23, 1997

Office of Generic Drugs
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: Minor Amendment , ANDA #40-183
Methylprednisolone Tablets, USP
4 mg

TELEPHONE AMENDMENT

Dear Sir

Please refer to our original ANDA, submitted February 29, 1996 and our amendments dated March 22, 1996, June 6, 1996, January 7, 1997, August 28, 1997, September 19, 1997, September 24, 1997, October 3, 1997, November 12, 1997 and your telephone call of December 5, 1997.

Below are listed the items as requested in your telephone call.

- Attachment I - Room temperature protocol as originally submitted

- Attachment II - Room temperature protocol as revised (will be used for future production batches)

- Attachment III - Room temperature protocol for pilot batches including old and new specifications

- Attachment IV - page 3 of 3 for 100 count room temperature stability

- To clarify the response to 2A
New impurity method was submitted as Attachment XVI in the response to the major deficiency. The supplement to the methods validation was submitted as Attachment XVII.

- To clarify the response to 2B
The analytical procedure was still in draft at the time of three month room temperature stability testing.

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DEC 24 1997
GENERIC DRUGS

- To clarify the response to 2C Attachment V - Revised method includes a notation for sample preparation that samples should be analyzed the same day of preparation. The data was regarded as bad due to the fact that at the next time point all impurities were within specifications.

This completes our response to the minor amendment issued. If I can be of further assistance or if you have any questions, please contact Rebecca Thurman or John Schultz at (704) 596-0516.

Sincerely,

Rebecca Thurman
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

December 9, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N /Am1

RE: Minor Amendment , ANDA 40-183
Methylprednisolone Tablets, USP
4 mg

Dear Sir

Please refer to the Vintge original ANDA, submitted February 29, 1996, amendments dated June 6, 1996, November 12, 1997, December 23, 1997 and January 28, 1998 and FDA letter dated February 5, 1998.

Enclosed you will find our response to the deficiency as outline in the FDA letter of February 5, 1998.

If I can be for further assistance or if you have any questions, please contact Rebecca Childers or John Dambrauskas at (704) 596-0516.

Sincerely,

Rebecca Childers
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

August 28, 1997

Office of Generic Drugs
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: Minor Amendment , ANDA #40-183
Methylprednisolone Tablets, USP
4 mg

FACSIMILE AMENDMENT

NOTE: The labeling is not included in the faxed response, however it is included in the hard copy being sent.

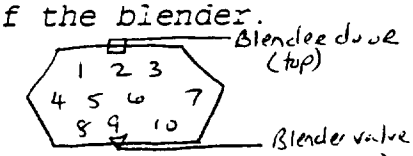
Dear Sir

Please refer to our original ANDA, submitted February 29, 1996 and our amendments dated March 22, 1996, June 6, 1996 and January 7, 1997 and your facsimile amendment dated July 30, 1997. Each of the points in your facsimile is stated, followed by our response.

A. Deficiencies

1. **Please explain if the granulation assay is performed on the final blend. Please provide a summary of the sampling plan for this test. In addition, please note that stage II assay testing of the granulation/blend is not acceptable. Please revise the in-process limits to only have stage I assay testing.**

Granulation assay is performed on the final blend. A sample is pulled from 10 locations in the blender. The sample from each location are tested for assay. The sample are from the following locations of the blender.
Samples 1,2,& 3 - Top of Blend Layer
Samples 4,5,6,7 - Middle of Blend Layer
Samples 8,9,10 - Bottom of Blend Layer



Attachment I - page 3 of 8 of master production record (sampling plan)
Attachment II - Revised in-process specifications

2. **Please explain if the impurity U-82, 040, as specified in the release of the finished product is the same as the impurity U-84,040 specified in the stability. If they are the same and this is a typo, please make the appropriate corrections to the application.**

The U-82,040 as specified in the finished product release forms was a typing error and has been corrected.

Attachment III - Revised finished product release

3. **You have indicated that the impurity assay method was re-investigated because of insufficient resolution between impurity peaks. You also specify that the new procedure is based on the impurity procedure used by the raw material supplier. However, your impurity specifications in the drug substance and the drug product (release and stability) are greater than those of the drug substance supplier. Please explain. We recommend that the impurities limits should be similar to the limits established by the drug substance supplier. The specifications should also include a limit for the individual unknown impurities. The limit for unknown impurities must be based on observed results. Also, please provide an updated COA from the raw material supplier.**

The impurity method described in the lab procedure for the raw material evaluates both in-process raw material impurities and raw material degradation products. While the in-process impurities should not increase over time, the degradation products may. When the raw material lot R001020 was tested, the total impurities were determined to be %. We have set the total impurity limit at % for the raw material based on these determined impurity results. The limits for the individual known impurities have been revised to more closely reflect the determined results (See revised Raw Material Specifications). The limit for any individual unknown impurity in raw material testing has been lowered from %.

In some products, it is not unusual for the active in tablets to have more degradation than the raw material because of the different conditions and excipients to which it is exposed. Therefore, we have allowed % over the raw material total impurity limit of % to compensate for any further degradation. The total impurities limits for finished products and stability samples is %. The limits for the individual known impurities have been adjusted from % for all

known impurities except U-84,040. The limit for this impurity will remain %. The limit for any unknown impurities found in finished product or stability samples has been revised from %.

Attachment III - Revised finished product release
Attachment IV - Revised raw material specifications and COAs

4. **Please explain why your impurity specifications for the drug product (release and stability) are greater than the impurity specifications for the drug substance. Impurities should not increase over time.**

Impurity limits for finished product and stability samples are frequently set higher than the limits for raw materials for several reasons. Often the tableting process can cause higher results of impurities in finished products than are seen in raw material samples. Also, in-process impurities are not expected to increase over time, but degradation products, which are also quantitated on this system, may increase. Because of this, the total impurity limit of % for raw material samples has been raised by % for finished product samples and stability samples. In addition, the limits for individual known impurities are slightly higher for tablet form testing than the newly adjusted raw material limits (See the revised Raw Material Specifications and the Finished Product Release forms). The limit for an unknown impurity will be % for both raw material testing and tablet form testing.

5. **Please explain why the impurity results on stability (reference Attachment XIII) are consistently less than impurities reported in the drug substance (reference Attachment III). In addition, please explain why there are specifications for eighteen individual impurities in the drug substance, but the drug product only has specifications for nine individual impurities.**

The impurity results for the methylprednisolone raw material lot R001020 have been determined to be greater than the impurity results for the finished product and stability samples. These results were confirmed by a second analyst, who prepared samples on another day using a different instrumentation. The impurity method has been completely validated and proven to be reliable and rugged, indicating perhaps these results are not due to the method of analysis. The high impurity results for the raw material may be due to the manner of storage of the retained sample. The results are unusual, but seem to be correct. However, if future raw material batches have higher impurity

results than corresponding finished products, the method will at that time be re-investigated. The impurities for the raw material samples and the tableted samples have very similar chromatograms with nearly the same number of impurities. Of the approximate 18 impurities that are detectable on this system, nine are known impurities. These nine individual known impurities are listed on finished product and stability forms. Other unknown impurities are also quantitated for finished products and stability samples. It is required on both finished product and stability sheets that none of these unknown impurities be greater than % . Also, all known and unknown impurities are summed and listed on these forms at the total impurities.

Attachment V - revised stability

6. **In Attachment X of this amendment, you have revised the raw material testing commitment as we have requested (one year for actives and two years for the inactives). However, on the drug substance COA in Attachment IV, the retest period is still identified as two years. Please revise accordingly.**

The retest dates on the COA were left at 2 years, because that was the retest period in the standard operating procedure at the time of release of the lot. The procedure has been revised to a retest period of one year for both active and inactives. All lots received and released from the effective date of the procedure will have the 1 year date. The 1 year retest date will not be made retroactive for lots released before the effective date of the procedure.

Attachment VI - Current procedure with 1 year retest date.

Labeling Deficiencies:

1. **GENERAL COMMENT**

We note that you have not submitted 12 copies of final printed container (100's, 500's and 1000's) and Unit-of-use Blister Pack (21's) labels. Please submit these labels and/or comment.

Attachment VII - Final printed container labels Vintage will not be using the unit of use blister pack labels

2. **UNIT-OF-USE BLISTER PACK (21's) - Submitted June 11, 1996.**

a. We note that you have included the comment, "Place pharmacy label here" on the container label and the carton labeling for this product. Please revise and/or comment.

Vintage will not be using the label for the blister packs. The statement will remain on the carton so that the pharmacist can dispense the unit-of-use blister packs in the carton. This statement also appears on the Medrol carton.

b. Please provide for our review and comment a fully assembled (without the tablets) unit dose blister package which includes the molded blister card and all proposed labeling components as it will appear in the marketplace. You need not provide the carton labeling.

Attachment VIII - Molded blister card with print. The insert will be placed in the carton along with the blister card

3. INSERT

a. GENERAL

We encourage the inclusion of "USP' in the established name of your drug product.

b. DESCRIPTION

Please revise the chemical name to be same as the second name appearing in USP 23.

c. WARNINGS

Increase the prominence of the subsection heading "Usage in pregnancy".

d. DOSAGE AND ADMINISTRATION

i. Delete and parenthesis from the heading of the Alternate Day Therapy subsection and replace with "alternate day therapy" throughout the text of this section.

ii. First sentence:

... 4 mg to 48 mg of methylprednisolone per...

iii. Alternate Day Therapy, item 4) - second sentence:

... a suppressed HPA... (add "a")

e. HOW SUPPLIED

i. We encourage the inclusion of the "Dispense in" statement, as found on your container labels (100's, 500's, 1000's)

ii. ...(59° - 86° F). [add "°" to "86"]

Please revise your unit-of-use blister pack (21's) configuration and you package insert labeling, as instructed above. Submit container labels and package insert labeling in final print and the revised unit-of-use blister pack (21's).

Attachment VII - final printed container labels
Attachment VIII - Unit-of-use blister pack
Attachment IX - revised insert

Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a) (8) (iv), please provide a side-by-side comparison with your last submission with all differences annotated and explained.

Attachment X - side-by-side comparisons

This completes our response to the facsimile amendment issued. If I can be of further assistance or if you have any questions, please contact Rebecca Thurman or John Schultz at (704) 596-0516.

Sincerely,

Rebecca Thurman
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

March 22, 1996

Office of Generic Drugs, CDER, FDA
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RECEIVED
MAR 25 1996

RE: Methylprednisolone Tablets USP, 4 mg
ANDA 40-183
Amendment

Dear Sir:

Please refer to our Abbreviated New Drug Application dated February 18, 1996 for Methylprednisolone Tablets, USP 4 mg ANDA# 40-183. Please refer also to your letter dated March 18, 1996.

In response to your letter, Vintage has enclosed manufacturing and packaging reconciliation and yield summaries to verify that the entire demonstration batch of Methylprednisolone Tablets USP, 4 mg was indeed packaged. Also included in the summary is the reference to page numbers in the submission where the data can be found.

Also included in the amendment is a revised "scale-up" production batch record and reprocessing record for tablets which is equal to the net yield of the demonstration batch. The tablets production record and reprocessing record will replace the tablets production record and reprocessing record previously submitted.

If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Mr. John Schultz, Assistant General Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

Rebecca A. Thurman
Manager, Regulatory Affairs

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

3/12/96

February 29, 1996

Office of Generic Drugs, CDER, FDA
Document Control Room, Rm 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Dear Sir:

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an original Abbreviated New Drug Application for:

Methylprednisolone Tablets, USP
4 mg

Vintage Pharmaceuticals, Inc. is registered as a manufacturer of controlled substances in schedules II, III, IV, and V, under DEA Registration No. RV0172976.

In-vivo and in-vitro bioequivalence studies are included in section VI.

The archival copy of the ANDA consists of four volumes. The review copy consists of two red-jacketed chemistry & manufacturing volumes and three separately bound, orange-jacketed bioequivalence volumes. All volumes contain a complete Table of Contents. The following items are included immediately following the NDA Form 356h:

-Prescription Status Statement
-Debarment/Conviction Certification
-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Mr. John Schultz, Assistant General Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

Rebecca A. Thurman
Manager, Regulatory Affairs